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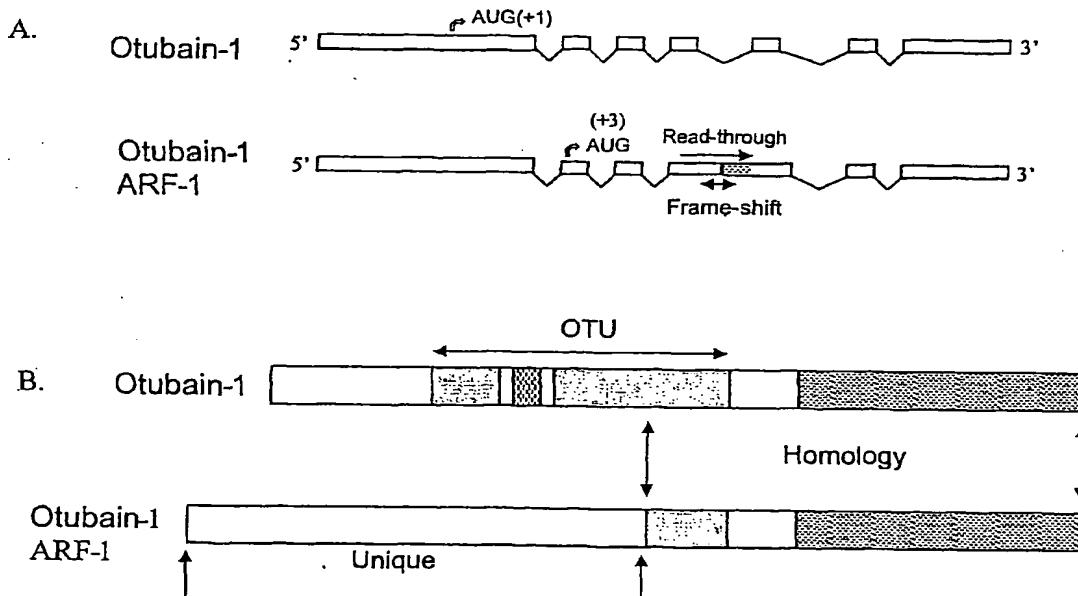
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(54) Title: A POLYPEPTIDE COMPLEX THAT REGULATES CELL CYCLE AND ANERGY ✓



(57) Abstract: An active ubiquitin E3 ligase, GRAIL, is crucial in the induction of anergy in cells of the immune system, and in the regulation of cellular proliferation. GRAIL is shown to associate with, and be regulated by Otubain isoforms, including OTUBAIN-1 (DOG, the Destabilizer of GRAIL) and an alternative reading frame splice variant of OTUBAIN-1 (SOG, the Stabilizer of GRAIL). These proteins play opposing roles in the regulation of GRAIL auto-ubiquitination and consequently on its ability to induce anergy and regulate cellular proliferation. DOG serves as an adaptor protein, recruiting the DUB USP8. One major substrate for USP8 is the Ras exchange factor Ras-GRF1, and this protein can be found in a complex with USP8 and GRAIL, which complex is ubiquitinated by GRAIL.

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